



TITLE:

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CITATION:

Markovic, Borislav. Primary chronic interstitial nephropathies followed by urinary tract tumors. 泌尿器科紀要 1974, 20(2): 63-69

ISSUE DATE:

1974-02

URL:

<http://hdl.handle.net/2433/121627>

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PRIMARY CHRONIC INTERSTITIAL NEPHROPATHIES FOLLOWED BY URINARY TRACT TUMORS

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The subject of this study is to investigate the circumstances and etiologic factors which have lead to the mass occurrence of endemic nephropathy in the Balkan as well as the pathomorphological characteristics on cellular and subcellular level, with the aim to discover and identify in other countries outside the Balkan.

INTRODUCTION

In 1953 the Bulgarian authors first made a systematic study on the mass occurrence of endemic nephropathy in two districts of the Balkan: Vraca and Mihailovgrad in the west Bulgaria. In 1956, the first report was made by Tančev and Coll. At the First International Congress of Nephrologists (Eviane, France), the Bulgarian scientists presented the paper saying that this nephropathy was followed by urinary tract tumor in approximately a thirds of autopsy cases. Investigation by Pukhlev (1970) cleared that 50 villages in above two districts were invaded by endemic nephropathy with high percentage of malignant urothelial alteration reaching 48% of the patients. In Yugoslavia, Petković and Coll, urologists, first noticed the frequent occurrence of urinary tract tumor on the basis of endemic nephropathy as well as the fact that the patients with this tumor developed chronic renal insufficiency in 40~43%. As far as the number of the patients is concerned, Yugoslavia showed the largest spread among the Balkan countries but smaller percentage of urinary tract tumor than Bulgaria. The Bulgarian and Yugoslavian authors agreed with the fact that all of these tumors were mostly localized at the upper uroepithelium. Histopathologically,

the tumors were malignant in most of the cases such as papillary carcinoma while benign in a small number of cases. These tumors could be solitary or multiple and unilateral or bilateral in the urinary tract.

Clinically established endemic nephropathy has fatal outcome in a period between one and two years on average. Up to now, no cured case of this disease was known. At the symposium on endemic nephropathy held at Serbian Academy of Science, Beograd, on 19 and 20th of November, 1970, 19,000 patients were registered from Yugoslavia, 5,000 to 6,000 from Bulgaria and 2,000 to 3,000 from Rumania. These numbers did not include the suspicious cases of endemic nephropathy whose number could be larger several times than the number of clinically manifest cases. These numbers also excluded children cases because it was unknown if they could be affected by endemic nephropathy. Bulgarian researchers, however, performed renal biopsy in children living in the area of endemic nephropathy and concluded that pathologic process in the kidney can develop in children in a subclinical form (Jurukova and Dimitrova, 1972).

MATERIALS AND METHODS

In the quoted Balkan countries, intensive denudation of some mountainous regions for last several years resulted in erosion of the silicate rocks of volcanic origin. The fine crushed material of these rocks could be carried away by streams and rivers, and along their courses, the material penetrates into drinking water of the populated areas if the underlying soil (alluvion) is suitable. These are usually primitive country wells

and their water level depends on that of the rivers. Chemical analysis of drinking water by us in the foci of endemic nephropathy showed high concentration of silicate (15~50 mg/L). The concentration varied depending on precipitation and the river water level. The silicate was present mostly in the form of microparticles and partly in the form of free silicic acid (ionized state). It originates from different silicate minerals: granite, feldspath, biotite, quartz. For chemical analysis on the content of heavy and light metals specimens of granite were taken from the rocks over the foci of endemic nephropathy which had been eroded and deposited into drinking water. In parallel with this analysis, chemical analysis of microelements was also performed and conclusion was established as to their presence in increasing but changeable concentrations in water (Marković and Lebedev, 1956).

In these urinary tract diseases, silicic acid is responsible for pathogenesis of the kidney lesions. Silicic acid is created in the processes of hydrolysis of these minerals in drinking water or in human body (Marković, 1967, 1970). We pointed out the importance of the rest content of magmatic silicate rocks of heavy and radioactive metals with blastomogenous properties (Ni, Cr, Ur, and so on) for pathogenic effects on urinary tract (Marković, 1972). For the explanation of high incidence of urinary tract tumors following endemic nephropathy in Bulgaria, special geographic and geochemical particularities of Bulgarian soil was considered. The mountainous districts (Stara planina) have ultrabasic geochemical structure rich in heavy metals (Ni, Cr, Ur, and so on) mixed with volcanic granite acid rocks containing a great deal of quartz. These areas are exposed to intensive erosive process. The rivers, Iskar and Ogosta, contain these materials already from the upper mountainous regions and become more remarkable in their lower courses.

Already in the first report of Makarow and Coll (1966) and in the later report from Bulgaria, spectral emission analysis of the organs such as liver, spleen and

kidney of the patients who died of endemic nephropathy, proved considerable concentrations of Ni, Cr, Al, and so on.

PATHOMORPHOLOGY OF SUBCELLULAR LEVEL

The kidney biopsy specimens from the patients of the early phase of endemic nephropathy were fixed in 1% OsO₄ and embedded in Epon 812. Sections were cut on a Sjöstrand Om U₂ ultramicrotome, stained with uranyl acetate and lead hydroxide. The samples were examined in a Philips EM 300 electron microscope at 80 to 100 kV.

The kidney tissue was analyzed for ultrastructure abnormalities in the interstitium, glomeruli, tubules, and blood vessels. The most striking abnormality was a focal increase of collagen fibers in the cortex and medulla. The collagen was usually noted as organized bundles of packed collagenous fibers.

Lesions of glomeruli, tubules, and blood vessels were of focal nature and simultaneous. The Bowman capsule was thickened due to hypertrophy of mesenchyma between the visceral and peripheral sheet. In the periglomerular stroma noted were the proliferation of fixed connective cells (histiocytes and fibroblasts) and the presence of strong bundles of collagenous fibers. In some glomeruli, proliferation was seen particularly around the vascular pole of Malpighian corpuscle. In the capillary ball of glomeruli, there was definite proliferation with numerous nuclei in the intercapillary mesenchyma. Proliferation of mesangial cells was noted between the basement membrane and endothelium, which was followed by an increased secretion of mesangial matrix filling the enlarged intercellular channels. The enlarged mesangial axis was transformed into a hypocellular hyaline mass. Both the basement membrane and the lamina densa were thickened and their endothelial cells were swollen. This caused narrowing of the capillary lumen leading to their complete obstruction.

In podocytes noted was the swelling and increase of cytoplasmic organelles of a

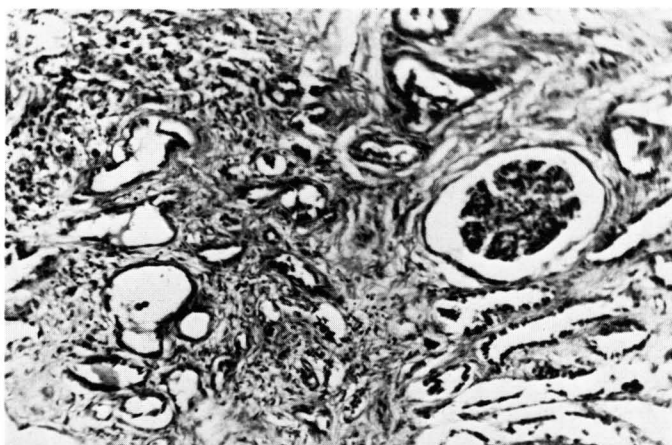
hyperactive type. Their foot processes were well preserved.

Some glomeruli were filled with homogeneous hyaline substance, and some of them demonstrated undifferentiated fibroblasts resembling mesenchymal cells in the hyalinized capillary ball.

In some glomeruli, the number of nuclei of endothelial cells was reduced in the capillary ball, and endothelium was atrophic. Partial atrophy and destruction of basement capillary membranes and intercapillary mesenchyma resulted in the defect in the capillary ball giving the

segmental appearance (lobulation).

The main changes in the tubules were seen in the proximal convoluted tubules. The basement membrane of the tubules was thickened and that of the interstitial side showed increase of collagen fibers. The osmiophilic inclusions were present exactly in the basement membrane. In the epithelial cells noted were hydropic and vacuolar degeneration as well as increase of cytosomes and cytoseresomes. In the epithelial cells close to the urinary pole of Malpighian corpuscles, focal cellular necrosis was seen.



Human endemic nephropathy

Fig. 1. Interstitial infiltration and sclerosis. Fibrous, hyalinized, thickened Bowman's capsule of the glomeruli. Tubular lumina are deformed, narrowed, and widened with low atrophic epithelium. Some tubuli are microcystically widened (Light microscope, 10×10 , HE).

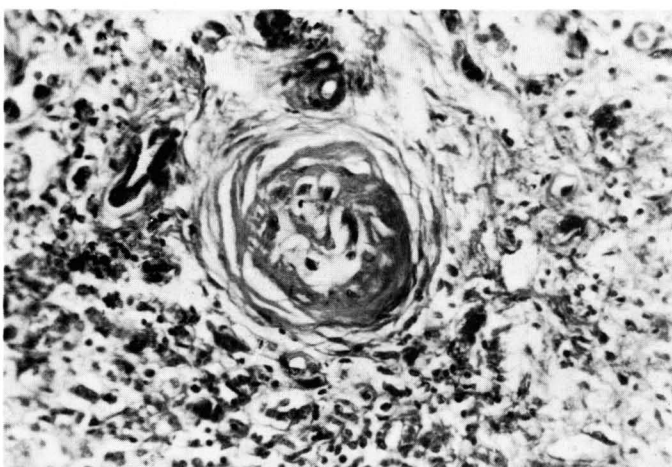


Fig. 2. Interstitial mononuclear infiltration and fibrosis. Glomeruli are in the phase of hyalinization and concentric retraction (10×23 , HE).

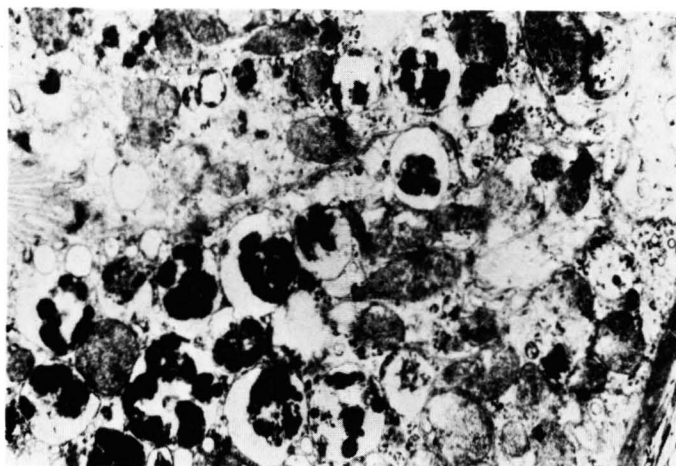


Fig. 3. Swollen mitochondria with light reduced mitochondrial matrix and content of "electron dense bodies". Some swollen mitochondria show the tendency to break up (Electron microscope, $\times 12,000$).

In some epithelial cells noted were the amorphous osmiophilic masses basally situated. In the mitochondria, there were fine granulated electron dense bodies of 1.0 to 0.5 microns in diameter (Fig. 3).

The bigger was the deposit of this osmiophilic inclusion, greater was the reduction in the density of mitochondrial matrix. Mitochondria got swollen and broken up, whose content finally being eliminated by potocytosis into the tubular lumen. Only vacuolar degeneration or atrophy of the distal tubular epithelium was observed. The basement membranes were thickened and an abundant deposition of homogeneous ground substance was observed in the interstitial space.

PATHOMORPHOLOGY ON CELLULAR LEVEL

Endemic nephropathy belongs to the group of primary chronic interstitial nephropathy, and its histopathological pictures present a separate nephrological unit. The histopathological features are characterized by pleomorphism of lesions, depending on type, quantity and duration of exposure to the pathogenic effect of causative agent as well as predisposition of a person under the exposure of the agents (Marković, 1967, 1970). A wide spectrum of the lesions as to histopathological features should be evaluated. For example, some cases were

conspicuous with inflammatory, proliferative, dystrophic, atrophic, and necrotic lesions; whereas in some other autopsy cases noted were only monotonous interstitial sclerosis associated either with discrete focal infiltration or with uniform atrophic parenchyma (Marković, 1972).

Intrarenal distribution of these lesions was unique in such a way as subcapsular and juxtamedullary parts of the cortex were most markedly involved. In these parts, notified were the intensive interstitial sclerosis with focal inflammatory infiltration of lymphocytes, plasma cells, eosinophils and mast cells. The focal mononuclear cell infiltration was most striking in the juxtamedullary part of the cortex. In the sclerotic subcapsular part of the cortex, most of glomeruli were hyalinized (Fig. 2). Some glomeruli showed thickened Bowman's capsule and slight proliferation of connective tissue at the intercapillary mesenchyma of the capillary ball. The number of tubules was reduced with atrophy of the epithelium. In some of the tubules, due to atrophy and necrosis of the epithelium, basement membrane and intertubular stroma were directly faced to their lumen. Microcystic formation was also seen (Fig. 1).

Blood vessel wall showed slight sclerotic changes but transiently. Subcortical part of the medullary pyramids as well as the

renal papillae was also affected by intensive sclerosis, but without inflammatory infiltration in the papillae. In the typical cases, the kidney became atrophic and weighed only 20 to 30 grams. Due to extreme nephrocirrhosis, the renal cortex could be reduced to several millimeters, while the medulla had relatively larger thickness than the cortex. The number of column of Bertin and pyramids was also reduced. When these changes were so remarkable it was difficult to recognize the kidney structures.

The kidney usually retained smoothly waved surface (Marković and Arambašić, 1971)

As mentioned above, the cortex was the site of the most intensive and most striking histopathological changes. Question might arise if the pathologic process be developed by intensive inflammatory proliferative lesions, or these lesions would be fibroplastic, or they would be developed with a discrete collagenosis. The fact was that the lesions started, as a rule, focally at the interstitium around some blood vessels, glomeruli and tubules in the cortex and led to nephrosclerosis. This pleomorphic lesions decreased toward the papillae which were affected only by hyalinization not associated with inflammatory proliferation or necrotic changes.

DISCUSSION

From many countries in the world, reports were made on the frequency of primary chronic interstitial nephropathies. Many factors were related with the diseases (Henderson, 1955) among which excessive use of analgesic substances was stressed (Spuhler and Zollinger, 1953). Sweden authors reported that a part of nephropathies due to abuse of phenacetin was followed by carcinoma of the real pelvis, although in some cases the abuse of analgesic substances could not be proved (Hultengern and Coll, 1965; Angervall and Coll, 1969).

There were some reports in which experimental papillary necrosis was provoked on the kidneys of the experimental animals

by phenacetin (Saker and Priscilla). In our experimental works with quartz and other silicates, no papillary necrosis was noted. By associated action of quartz and phenacetin, however, we succeeded in producing all other lesions in the kidney besides papillary necrosis typical for analgesic nephropathy. Based on the experimental studies, we stressed not only the importance of phenacetin and other analgesics in pathogenesis of these nephropathies but also the importance of reactive silicates on occurrence of interstitial lesions which is a prominent histopathological feature leading to dystrophic-atrophic lesions on parenchyma (Marković, 1971). In explanation of the occurrence of these urinary tract diseases in the countries where they have been reported, we emphasized the importance of geochemical soil structure as well as the environmental factors.

In some countries, intensity of denudation and erosion of soil was not proved as in the Balkan countries. Therefore, the mass occurrence could not be expected in these countries, but the frequency of analgesic nephropathies was already designated as an endemic occurrence (Sweden, Denmark, Canada, and other countries). In Canada, most of chronic nephropathies were reported from the east part where wood industry had been developed. Northeast part of Australia, New Zeland, and South-Afric Union are similar countries concerning geochemical soil structure with the Balkan nations.

North Scandinavia countries, Sweden and Norway are situated on the granite soil. In these countries, the erosive process does not advance by denudation. Poor vegetation due to severe climatic conditions and rich atmospheric precipitations promotes micro-erosion of the rocks and their content penetrates into drinking water.

In Denmark, Holland and North Germany, the soil contains granite rocks which are also subjected to microerosive process. In Switzerland, the nephropathy might be expected to occur in the western part of the country having volcanic granite rocks contrary to the eastern part having limestone.

We are now sure that in the Balkan countries endemic nephropathy is not always associated with urinary tract cancer and that malignancy is not always the outcome of endemic nephropathy even in the disseminated area.

It is also the fact that all silicates are not nephrotoxic (Marković, 1970; Newbern and Willson, 1970), just as all heavy metals are not blastomogenic. When explaining etiology of these urinary tract diseases and frequent occurrence in certain countries, we have to consider all the factors such as geophysic, geochemic, hydrologic of the soil as well as the results of clinical (Marković, 1970) and pathomorphological investigation on cellular and subcellular level. The changes in mitochondria of the epithelium (electron dense bodies) in the proximal part of tubules of the needle biopsy specimen are of special diagnostic importance. These changes were proved by experimental work of Policard and Coll (1960). In our experiment, animals were fed with quartz suspension (particles of 2-3 microns, 100 mg/L) under physiological circumstances for a period of 3-6 months and the identical changes were obtained in the kidney.

Whenever these changes in mitochondria are found, intoxication by silicate has to be thought first. We stressed the importance of renal biopsy of the patients who have been under the direct exposure of pathogenic silicate agent. The absence of these changes in mitochondria does not rule out the silicate etiology in endemic nephropathy, because the renal interstitial changes could be developed under the minimal content of reactive SiO_2 in drinking water mostly without polymerization in mitochondria of the epithelium (Marković, 1972).

SUMMARY

During the last decades, mass occurrence of a chronic kidney disease, endemic nephropathy, was recognized in some regions of the Balkan countries. In Bulgarian area, this nephropathy was accompanied with a high percentage of urinary tract tumors

mostly of malignant nature. In Yugoslavia, endemic nephropathy was followed by a smaller percentage of urinary tract tumors, while in Rumania the first cases of this kind of tumors were recently reported.

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(Accepted 1973. 5. 29)

